Modern Pharmaceutics

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edited by

GILBERT S. BANKER
University of Minnesota
Minneapolis, Minnesota

CHRISTOPHER T. RHODES
University of Rhode Island
Kingston, Rhode Island

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Parenteral Products

JAMES C. BOYLAN
Abbott Laboratories, Abbott Park, Illinois

ALAN L. FITES
Eli Lilly and Company, Indianapolis, Indiana

I. INTRODUCTION

The earliest foundation for injectable products can be traced to Hippocrates, who recommended strict exclusion of certain unsanitary agents during the treatment of wounds [1]. It was not until the seventeenth century, however, that the circulatory system was described and the first intravenous injections were made. In 1628, William Harvey presented his historic thesis on the circulation of blood. In 1657, Sir Christopher Wren successfully injected opium intravenously into dogs using a bladder connected to a small tube. This was followed in 1665 by the first successful intravenous injection of a drug into a human being by Major, Elsholtz, and Fabricius [2,3].

Sterilization is an essential prerequisite of safe parenteral administration. In 1782, Scheele preserved vinegar by boiling it in closed vessels, leading the way to heat sterilization of products [2]. Robert Koch, in collaboration with Gaffky and Loffler, experimented with steam as a disinfectant in 1881 [4].

Alexander Wood of Edinburgh, Scotland, gave the first successful subcutaneous injection using a hypodermic syringe in 1853. In 1894, a German living in Paris invented the modern hypodermic syringe [2]. The basis for the development of modern intravenous therapy was laid in the early nineteenth century by Scheele and Dieffenbach and two veterinarians, Viborg and Hertwig. The latter carried out carefully designed experiments on horses [5].

The first official injection (morphine) appeared in the British Pharmacopoeia (BP) of 1867. It was not until 1898 when cocaine was added to the BP that sterilization was attempted. In this country the first official injections may be found in the National Formulary (NF), published in 1926. Monographs were included for seven sterile glass-sealed ampoules. The United States Pharmacopeia (USP) published in the same year contained a chapter on sterilization but no monographs for ampoules. The current USP contains monographs for 470 injectable products.

Parenteral administration of drugs by intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes is now an established and essential part of medical practice, although the parenteral route is relatively new when one considers the long history of drugs. Advantages for parenterally administered drugs include primarily the following: rapid onset, predictable effect, predictable and nearly complete bioavailability, and avoidance of the gastrointestinal tract (GIT), hence the problems of variable absorption, drug inactivation, and GI distress. In addition, the parenteral route provides reliable drug administration in very ill or comatose patients.

The pharmaceutical industry directs considerable effort toward maximizing the usefulness and reliability of oral dosage forms in an effort to minimize the need for parenteral administration. Factors that contribute to this include certain disadvantages of the parenteral route, including the frequent pain and discomfort of injections with all the psychological fears associated with "the needle," plus the realization that an incorrect drug or dose is often harder or impossible to counteract when it has been given parenterally (particularly intravenously) rather than orally.

In recent years, parenteral dosage forms, especially IV forms, have gained immensely in use. The reasons for this growth are many and varied, but they can be summed up as (1) new and better parenteral administration techniques; (2) new forms of nutritional therapy such as intravenous lipids, amino acids, and trace metals; (3) the need for simultaneous administration of multiple drugs in hospitalized patients on IV therapy, and (4) the extension of parenteral therapy into the home. Parenteral systems have been developed in the last decade or two that will maintain an unconscious or critically ill patient for many months, even years, at a proper hydration level and balanced electrolyte state, while providing balanced nutrition sufficient to maintain tissue synthesis and support.

Many important drugs are available only as parenteral dosage forms. Notable among these are insulin, several cephalosporin antibiotic products, and drugs such as heparin, protamine, and glucagon. In addition, other drugs such as lidocaine hydrochloride and many anticancer products are used principally as parenterals. Reasons that certain drugs are relegated largely or exclusively to the parenteral route are very inefficient or unreliable absorption from the GIT, destruction or inactivation in the GIT, extensive mucosal or first-pass metabolism following oral administration or clinical need in particular medical situations for rapid, assured high blood and tissue levels.

Along with this astounding growth in the use of parenteral medications, the hospital pharmacist has developed from a health professional who had little real contact and only a passing acquaintance with parenteral products to a very knowledgeable, key individual in most hospitals, having responsibility for hospital-wide IV admixture programs, parenteral unit-dose packaging, and often central surgical supply. By choice, by expertise, and by responsibility the pharmacist as accumulated the greatest fund of information regarding parenteral drugs—not only their clinical use, but also their stability, incompatibilities, methods of handling and admixture, and proper packaging. More and more, nurses and physicians are looking to the pharmacist for guidance on parenteral products.

To support the institutional pharmacist in preparing IV admixtures (which typically involves adding one or more drugs to large-volume parenteral fluids), equipment manufacturers have designed laminar flow units, transfer devices, and filters specifically adaptable to a variety of hospital programs.

The nurse and physician have certainly not been forgotten either. A wide spectrum of IV and IM administation devices and aids have been made available in recent years for bedside use. Many innovative practitioners have made suggestions to industry that have resulted in product or technique improvements, particularly in IV therapy.

II. ROUTES OF PARENTERAL ADMINISTRATION

The principal routes of parenteral administration of drugs to achieve systemic effects are (1) subcutaneous, (2) intramuscular, and (3) intravenous; other more specialized routes are (4) intrathecal, (5) intracisternal, (6) intra-arterial, (7) intraspinal, and (8) intradermal. The intradermal route is not typically used to achieve systemic drug effects. The similarities and differences of the routes or their definitions are highlighted in Table 1. The major routes will be discussed separately.

A. The Subcutaneous Route

Lying immediately under the skin is a layer of fat, the superficial fascia (see Fig. 1 in Chapter 8), that lends itself to safe administration of a great variety of drugs, including vaccines, insulin, scopolamine, and epinephrine. Subcutaneous (SC; also SQ or sub-Q) injections are usually administered in volumes up to 2 ml using a $\frac{1}{2}$- to 1-in. 22-gauge (or smaller) needle. Care must be taken to ensure that the needle is not in a vein. This is done by lightly pulling back on the syringe plunger (aspiration) before making the injection. If the needle is inadvertently located in a vein, blood will appear in the syringe and the injection should not be made. The injection site may be massaged after injection to facilitate drug absorption. Drugs given by this route will have a slower onset of action than by the IM or IV routes, and total absorption may also be less.

Sometimes dextrose or electrolyte solutions are given subcutaneously in amounts from 250 to 1000 ml. This technique, called hypodermoclysis, is used when veins are unavailable or difficult to use for further medication. Irritation of the tissue is a danger with this technique. Administration of the enzyme hyaluronidase can help by increasing absorption and decreasing tissue distention. Irritating drugs and vasocontrictors can lead to abscesses, necrosis, or inflammation when given subcutaneously. Body sites suitable for SC administration include most portions of the arms and legs plus the abdomen. When daily or frequent administration is required, the injection site can and should be continuously changed or rotated, especially by diabetic patients self-administering insulin.

B. The Intramuscular Route

The IM route of administration is second only to the IV route in rapidity of onset of systemic action. Injections are made into the striated muscle fibers that lie beneath the subcutaneous layer. The principal sites of injection are the gluteal (buttocks), deltoid (upper arm), and vastus lateralis (lateral thigh) muscles. The usual volumes injected range from 1.0 to 3.0 ml, with volumes up to 10.0 ml sometimes being given (in divided doses) in the gluteal or thigh areas (Table 1). It is again important to aspirate before injecting to ensure that the drug will not be administered intravenously. Needles used in administering IM injections range from 1 to $1\frac{1}{2}$ in. and 19 to 22 gauge, the most common being $1\frac{1}{2}$ in. and 22 gauge.

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